FORM PTO-1390 (REV. 11-94)	U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE	ATTORNEY'S DOCKET NUMBER
TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US)		7914-082

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/EP00/01471	February 23, 2000	March 2, 1999 09/913891

TITLE OF INVENTION
A PROCESS FOR THE PREPARATION OF TAXANES FROM 10-DEACETYLBACCATIN III

APPLICANT(S) FOR DO/EO/US
BOMBARDELLI, Ezio

Applicant herewith submits to the United States Designated/ Elected Office (DO/EO/US) the following items under 35 U.S.C. 371:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.

2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.

3. ☒ This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).

4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.

5. ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. ☐ is transmitted herewith (required only if not transmitted by the international Bureau).
   b. ☒ has been transmitted by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US)

6. ☐ A translation of the International Application into English (35 U.S.C. 371(c)(2)) with Certificate of Verification.

7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ have been transmitted by the International Bureaus.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☒ have not been made and will not be made.

8. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 37(c)(3)).

9. ☒ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)), executed.

10. ☒ The International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern document(s) or information included:

11. ☒ An Information Disclosure Statement under 37 CFR 1.97 and 1.98 with copies of the references.

12. ☒ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.

13. ☒ A FIRST preliminary amendment.
    ☐ A SECOND or SUBSEQUENT preliminary amendment.

14. ☐ A substitute specification.

15. ☐ A change of power of attorney and/or address letter.

16. ☐ Other items or information:

INTERNATIONAL APPLICATION NO. PCT/EP99/09854 09/913891	INTERNATIONAL FILING DATE December 13, 1999

17. ☒ The U.S. National Fee (35 U.S.C. 371(c)(1)) and other fees as follows:

CLAIMS				
(1)FOR	(2)NUMBER FILED	(3)NUMBER EXTRA	(4)RATE	(5)CALCULATIONS
TOTAL CLAIMS	11 - 20	0	X $ 18.00	$ 0.00
INDEPENDENT CLAIMS	2 - 3	1	X $ 80.00	0.00
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ $ 270.00	☐

BASIC NATIONAL FEE (37 CFR 1.492(a)(1)-(5)): **CHECK ONE BOX ONLY** ☐ International preliminary examination fee paid to USPTO (37 CFR 1.482) . . . . . $ 690	
☐ No international preliminary examination fee paid to USPTO (37 CFR 1.482) but international search fee paid to USPTO (37 CFR 1.445(a)(2)) . . . . . $ 710	
☐ Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO $1000	$
☐ International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(2) to (4) . . . . . $ 100	$
☒ Filing with EPO or JPO search report . . . . . $ 860	$ 860.00
Surcharge of $130.00 for furnishing the National fee or oath or declaration later than 20 30 mos. from the earliest claimed priority date (37 CFR 1.492(e)).	
TOTAL OF ABOVE CALCULATIONS	= 860.00
Reduction by 1/2 for filing by small entity, if applicable. Affidavit must be filed also. (Note 37 CFR 1.9, 1.27, 1.28).	- $ 0.00
SUBTOTAL	= 860.00
Processing fee of $130.00 for furnishing the English Translation later than 20 30 mos. from the earliest claimed priority date (37 CFR 1.492(f)).	+
0 TOTAL FEES ENCLOSED	$ 860.00

a. ☐ A check in the amount of $__ to cover the above fees is enclosed.

b. ☒ Please charge Deposit Account No. 16-1150 in the amount of $940.00 to cover the above fees. A copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 16-1150. A copy of this sheet is enclosed.

18. ☐ Other instructions

n/a

19. ☒ All correspondence for this application should be mailed to

PENNIE & EDMONDS LLP
1667 K STREET, N.W.
WASHINGTON, D.C. 20006

20. ☒ All telephone inquiries should be made to (202) 496-4400

Thomas G. Rowan	Paul E. Bell (33,628) for Thomas G. Rowan	34,419	August 17, 2001
NAME	SIGNATURE	REGISTRATION NUMBER	DATE

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of: E. BOMBARDELLI

National Stage of PCT/EP00/01471

Group Art Unit: Unassigned

Filed: August 16, 2001

Examiner: Unassigned

For: A PROCESS FOR THE PREPARATION OF TAXANES FROM 10-DEACETYLBACCATIN III

Attorney Docket No.: 7914-082

PRELIMINARY AMENDMENT

Box PATENT APPLICATION
Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Please enter the following amendments and remarks into the file of the above-identified application prior to the examination thereof.

IN THE SPECIFICATION

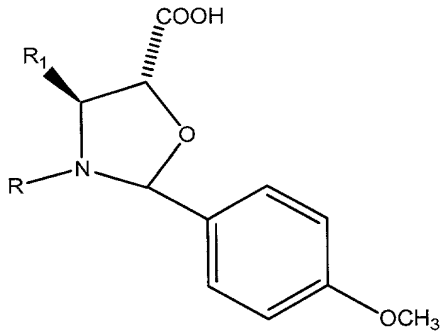
Marked up versions of all revised paragraphs showing insertions and deletions are included in Appendix A.

IN THE ABSTRACT

A marked up versions of the abstract showing insertions and deletions are included in Appendix A.

Please add the following abstract:

---A process for the preparation of taxane derivatives by reacting 10-deacetylbaccatin III protected at the 7- and 10- positions with trichloroacetyl groups with a compound of formula



and subsequent removal of the protective groups and hydrolysis of the oxazolidine ring.--

IN THE SPECIFICATION

Marked up versions of all revised paragraphs showing insertions and deletions are included in Appendix B.

Replace the paragraph starting at page 1, line 1 with the following text:

--TECHNICAL FIELD

The present invention relates to a process for the preparation of taxanes from 10-deacetylbaccatin III.--

Replace the paragraph starting at page 1, line 3 with the following text:

--BACKGROUND OF THE INVENTION

Paclitaxel is a known antitumor drug with taxan structure, whose industrial preparation is particularly complex.--

Replace the paragraph starting at page 2, line 30 with the following text:

--SUMMARY OF THE INVENTION

It has now been found a process for the preparation of taxanes, in particular Paclitaxel and Docetaxel, which attains a higher yield than known methods.--

Replace the paragraph starting at page 5, line 1 with the following text:

--DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The process of the invention differs from those of the prior art in that the reaction sequence used provides a simpler route than those processes cited above and a remarkable improvement in the obtained yields.--

Replace the paragraph starting at page 10, line 1 with the following text:

--CLAIMS

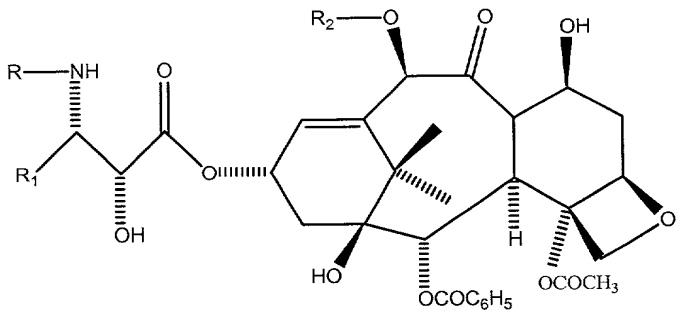
What is claimed is:--

IN THE CLAIMS

A complete listing of the currently pending claims is provided in Appendix C for the Examiners convenience.

Please cancel claims 1-9 and add the following new claims:

10. (New)A process for preparing a compound of formula I

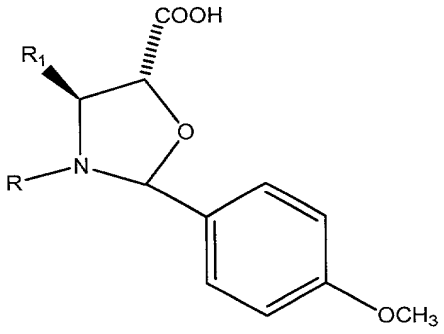


(I)

wherein R is a *tert*-butoxycarbonyl, benzoyl, or straight or branched chain alkyl carbonyl group; R_1 is a phenyl or a straight or branched alkyl or alkenyl group; and R_2 is hydrogen or an acetyl group comprising

(a) simultaneously protecting the C-7 and C-10 hydroxyl groups of 10-deacetylbaccatin III with trichloroacetyl groups to provide a protected 10-deacetylbaccatin III,

(b) esterifying the C-13 hydroxyl group of the protected 10-deacetylbaccatin III with an oxazolidine 5-carboxylic acid of formula II



(II)

wherein R is a *tert*-butoxycarbonyl, benzoyl, or straight or branched chain alkyl carbonyl group; R_1 is a phenyl or a straight or branched alkyl or alkenyl group to provide a protected C-13 esterified 10-deacetylbaccatin III having an oxazolidine ring at the C-13 position;

(c) removing the trichloroacetyl groups from the protected C-13 esterified 10-deacetylbaccatin III to provide a C-13 esterified 10-deacetylbaccatin III;

(d) optionally acetylating the C-10 hydroxyl group of the C-13 esterified 10-deacetylbaccatin III; and

(e) hydrolyzing the oxazlodine ring of the protected C-13 esterified 10-deacetylbaccatin III in the presence of an acid.

11. (New) The process of claim 10, wherein step (b) is carried out in the presence of a condensing agent and a base.

12. (New) The process of claim 11, wherein the condensing agent is dicyclohexylcarbodiimide.

13. (New) The process of claim 12, wherein the base is pyridine.

14. (New) The process of claim 10, wherein step (c) is carried out using NH_4OH/NH_4Cl in an aliphatic solvent.

15. (New) The process of claim 10, wherein step (d) is carried out by reacting the C-13 esterified 10-deacetylbaccatin III withacetic anhydride in the presence of a cerium III, scandium, or ytterbium salt.

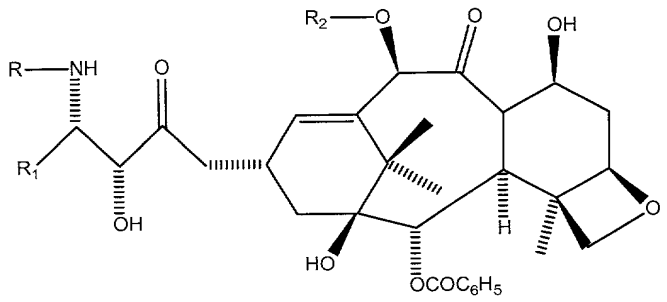
16. (New) The process of claim 10, wherein step (e) is carried out by reacting the protected C-13 esterified 10-deacetylbaccatin III with an organic acid or an inorganic acid in an aliphatic alcohol or tetrahydrofuran.

17. (New) The process of claim 16, wherein the acid is formic acid.

18. (New) The process of claim 1, wherein R is a benzoyl group, R_1 is a phenyl group, and R_2 is an acetyl group.

19. (New) The process of claim 1, wherein R is *tert*-butoxycarbonyl group, R_1 is a phenyl group, and R_2 is a hydrogen.

20. (New) A compound of Formula (IV)



(IV)

wherein R is a *tert*-butoxycarbonyl, benzoyl, or straight or branched chain alkyl carbonyl group; R_1 is a phenyl or a straight or branched alkyl or alkenyl group; and R_2 is hydrogen or an acetyl group.

REMARKS

New claims 10-20 are pending in this application for the Examiner's review and consideration. Applicants have amended the specification and claims to conform with U.S. patent practice and to more clearly recite the invention. As no new matter has been added herein, these changes should be entered.

Respectfully submitted,

(45,627)

for Thomas G. Rowan

Date August 17, 2001

Thomas G. Rowan (Reg. No. 34,419)

PENNIE & EDMONDS LLP
1667 K Street, N.W.
Washington, DC 20006

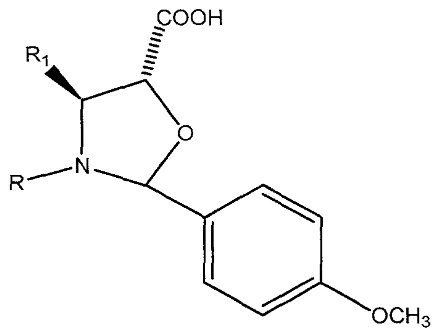
(202) 496-4400

Appendix A

Changes to the Abstract

Please add the following abstract:

---A process for the preparation of taxane derivatives by reacting 10-deacetylbaccatin III protected at the 7- and 10- positions with trichloroacetyl groups with a compound of formula



and subsequent removal of the protective groups and hydrolysis of the oxazolidine ring.--

Appendix B

Changes to the Specification

The paragraph at page 1, line 4 is revised as follows:

The paragraph at page 1, line 1 is revised as follows:

--TECHNICAL FIELD

The present invention relates to a process for the preparation of taxanes from 10-deacetylbaccatin III.--

The paragraph at page 1, line 3 is revised as follows:

--BACKGROUND OF THE INVENTION

Paclitaxel is a known antitumor drug with taxan structure, whose industrial preparation is particularly complex.--

The paragraph at page 2, line 30 is revised as follows:

--SUMMARY OF THE INVENTION

It has now been found a process for the preparation of taxanes, in particular Paclitaxel and Docetaxel, which attains a higher yield than known methods.--

The paragraph at page 5, line 1 is revised as follows:

--DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The process of the invention differs from those of the prior art in that the reaction sequence used provides a simpler route than those processes cited above and a remarkable improvement in the obtained yields.--

The paragraph at page 10, line 1 is revised as follows:

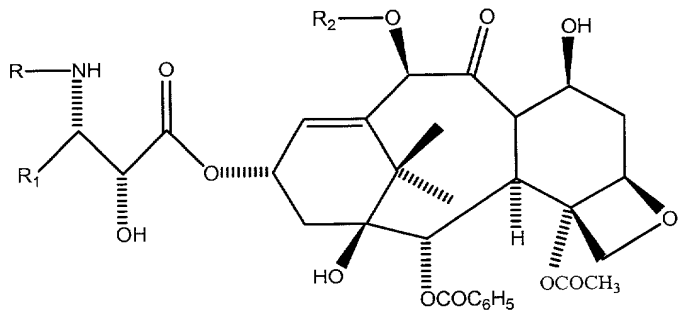
--CLAIMS

What is claimed is:--

Appendix C

Currently Pending Claims

10. (New) A process for preparing a compound of formula I

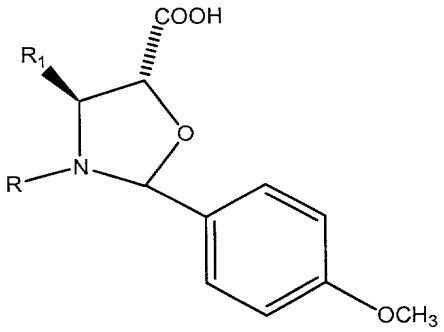


(I)

wherein R is a *tert*-butoxycarbonyl, benzoyl, or straight or branched chain alkyl carbonyl group; R_1 is a phenyl or a straight or branched alkyl or alkenyl group; and R_2 is hydrogen or an acetyl group comprising

(a) simultaneously protecting the C-7 and C-10 hydroxyl groups of 10-deacetylbaccatin III with trichloroacetyl groups to provide a protected 10-deacetylbaccatin III,

(b) esterifying the C-13 hydroxyl group of the protected 10-deacetylbaccatin III with an oxazolidine 5-carboxylic acid of formula II



(II)

wherein R is a *tert*-butoxycarbonyl, benzoyl, or straight or branched chain alkyl carbonyl group; R_1 is a phenyl or a straight or branched alkyl or alkenyl group to provide a protected C-13 esterified 10-deacetylbaccatin III having an oxazolidine ring at the C-13 position;

(c) removing the trichloroacetyl groups from the protected C-13 esterified 10-deacetylbaccatin III to provide a C-13 esterified 10-deacetylbaccatin III;

(d) optionally acetylating the C-10 hydroxyl group of the C-13 esterified 10-deacetylbaccatin III to provide a C-13 esterified baccatinn III; and

(e) hydrolyzing the oxazlodine ring of the protected C-13 esterified 10-deacetylbaccatin III or the C-13 esterified baccatinn III in the presence of an acid to provide the compound of formula I.

11. (New) The process of claim 10, wherein step (b) is carried out in the presence of a condensing agent and a base.

12. (New) The process of claim 11, wherein the condensing agent is dicyclohexylcarbodiimide.

13. (New) The process of claim 12, wherein the base is pyridine.

14. (New) The process of claim 10, wherein step (c) is carried out using NH_4OH/NH_4Cl in an aliphatic solvent.

15. (New) The process of claim 10, wherein step (d) is carried out by reacting the C-13 esterified 10-deacetylbaccatin III with acetic anhydride in the presence of a cerium III, scandium, or ytterbium salt.

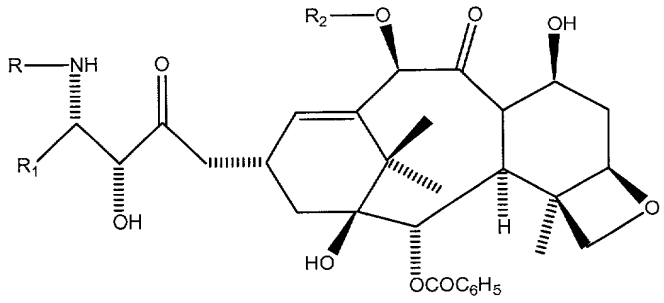
16. (New) The process of claim 10, wherein step (e) is carried out by reacting the protected C-13 esterified 10-deacetylbaccatin III or the C-13 esterified baccatinn III with an organic acid or inorganic acid in an aliphatic alcohol or tetrahydrofuran.

17. (New) The process of claim 16, wherein the acid is formic acid.

18. (New) The process of claim 1, wherein R is a benzoyl group, R_1 is a phenyl group, and R_2 is an acetyl group.

19. (New) The process of claim 1, wherein R is *tert*-butoxycarbonyl group, R_1 is a phenyl group, and R_2 is a hydrogen.

20. (New) A compound of Formula (IV)



(IV)

wherein R is a *tert*-butoxycarbonyl, benzoyl, or straight or branched chain alkyl carbonyl group; R_1 is a phenyl or a straight or branched alkyl or alkenyl group; and R_2 is hydrogen or an acetyl group.

A PROCESS FOR THE PREPARATION OF TAXANES FROM 10-DEACETYLBACCATIN III

The present invention relates to a process for the preparation of taxanes from 10-deacetylbaccatin III.

Paclitaxel is a known antitumor drug with taxan structure, whose industrial preparation is particularly complex.

Paclitaxel was first isolated by extraction from the trunk barks of *Taxus brevifolia*, and it is at present synthesized starting from 10-deacetylbaccatin III, an intermediate present in the leaves of different species of taxus, particularly in those of *Taxus baccata* L., thereby overcoming the environmental problems connected with the availability of bark of T. brevifolia.

A number of synthetic methods are reported in literature: US Re. 34,277 (reissue of US 4,924,011) discloses the semi-synthesis of Paclitaxel starting from 10-deacetylbaccatin III protected at the C-7 hydroxyl group with a trialkylsilyl group, in particular triethylsilyl, and at the 10- position with an acetyl group. In WO 98/08832, the protection of the C-7 hydroxyl group is carried out using a trichloroacetyl group. The thus protected baccatin III derivative is reacted with acetyl bromide and, subsequently, with the suitable phenylisoserine derivative to obtain Paclitaxel, following deprotection of the hydroxyl groups at 7 and 2' and benzoylation of the amine.

In WO 93/06094, Paclitaxel is prepared by reacting a beta-lactam-type compound with 7-triethylsilyl-baccatin III. The desired product is obtained by deprotection in acid medium.

In US 5 476 954, the synthesis of Paclitaxel is carried out starting from 10-deacetylbaccatin III,

protecting the C-7 hydroxyl with 2,2,2-trichloroethoxycarbonyl (Troc) and the C-10 hydroxyl with Troc or with an acetyl group.

It is therefore evident that the critical step for the synthesis of Paclitaxel is the selective esterification at C-7 with a group easily and selectively removable. Until now, 7-triethylsilyl-deacetylbaccatin III has been considered the key intermediate. The yield reported for the derivatization of 10-deacetylbaccatin III to 7-triethylsilyl-10-deacetylbaccatin III is about 85%, using 5 to 20 mols of silylating agent. The yield of the subsequent acetylation to give 7-triethylsilylbaccatin III is also about 85%.

US 5 621 121 and US 5 637 723 disclose the synthesis of taxanes, including Paclitaxel, by reacting suitably protected baccatin III or 10-deacetylbaccatin III with oxazolidine-5-carboxylic acids bearing at the 2- position a phenyl group substituted with alkoxy groups (US 5 621 121) or with trihaloalkyl groups, in particular trichloromethyl (US 5 637 723), followed by deprotection by opening of the oxazolidine ring.

The protective groups considered particularly suitable comprise silyl, 2,2,2-trichloroethoxycarbonyl or 2-(2(trichloromethyl)propoxy)carbonyl groups.

Substantially the same methods can also be used for the preparation of Docetaxel, another known taxan derivative widely used in clinics.

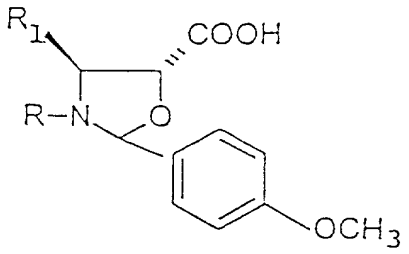
It has now been found a process for the preparation of taxanes, in particular Paclitaxel and Docetaxel, which attains higher yields than the known methods.

The process of the invention, shown in the following Scheme, comprises:

a) simultaneous protection of the hydroxyl groups at the 7- and 10- positions of 10-deacetylbaccatin III with

trichloroacetyl groups.

b) subsequent esterification of the hydroxyl at the 13-position by reaction with a compound of formula (VII):



(VII)

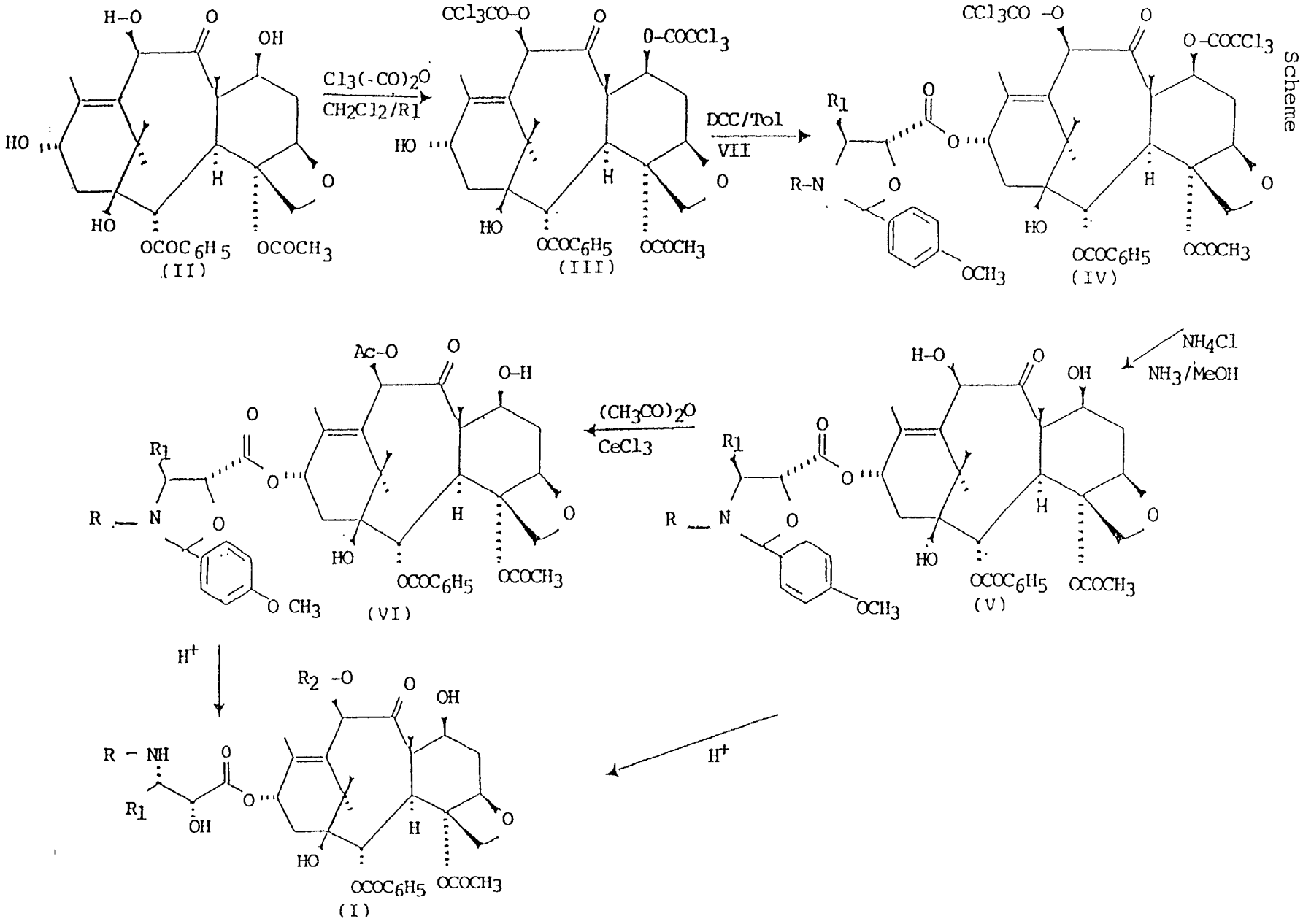
wherein R is tert.butoxycarbonyl, benzoyl or the residue of a straight or branched aliphatic acid and R_1 is phenyl or a straight or branched alkyl or alkenyl;

c) removal of the trichloroacetic protective groups;

d) optional selective acetylation of the hydroxyl at the 10- position, for those compounds in which R_2 is acetyl;

e) acid hydrolysis of the oxazolidine ring.

Scheme



The process of the invention differs from those of the prior art in that the reaction sequence used provides a simpler route than the known processes cited above and a remarkable improvement in the obtained yields.

Step a) is conventionally effected with trichloroacetic anhydride in suitable solvents and in the presence of bases such as pyridine, triethylamine and the like.

The esterification with the oxazolidine-5-carboxylic acid derivative is carried out in the presence of a condensing agent such as dicyclohexylcarbodiimide or other known reagents, in an anhydrous organic solvent, preferably aliphatic, aromatic or chlorinated hydrocarbons, at temperatures ranging from room temperature to the boiling temperature of the solvent.

The resulting oxazolidine ester is then deprotected by removing the 7- and 10- trichloroacetyl groups by treatment with NH_4OH/NH_4Cl in aliphatic alcohols, preferably methanol.

The selective acetylation of the hydroxyl at the 10-position is carried out with acetic anhydride in the presence of cerium III, scandium or ytterbium salts, in a solvent such as tetrahydrofuran, dichloromethane, ethyl acetate, at temperatures ranging from 5 to 40°C.

The treatment with organic or inorganic acids in solvents such as methanol, ethanol, tetrahydrofuran, at temperatures ranging from about -2 to +2°C, yields the desired taxane derivatives. The use of formic acid in tetrahydrofuran at a temperature of 0°C is particularly preferred.

The oxazolidine intermediates are known or can be prepared with known methods, by reaction of an isoserine ester with 4-methoxy-benzaldehyde.

The choice of anisic aldehyde proved to be

particularly important for the formation of the oxazolidine, in that oxazolidine acid, contrary to the methods described in US 5 621 121, 5 637 723 (Rhône-Poulenc Rorer), and in 5 821 363 (UpJohn), can easily be crystallized and adjusted to a 95:5 isomer ratio, which is extremely useful and advantageous for the subsequent step. Furthermore, the oxazolidine carboxylic acid obtainable with anisic aldehyde is particularly stable during the deprotection of the trichloroacetic ester and the subsequent acetylation step. In these conditions, 2,4-dimethoxybenzaldehyde used in US 5 821 363 or chloral or p-trichloromethyl-benzaldehyde as described in US 5 621 121 and 5 637 723 (Rhône-Poulenc Rorer) are not sufficiently stable.

The process of the invention, in addition to Paclitaxel (R = benzoyl, R_1 = phenyl) and Docetaxel (R = tert.butoxycarbonyl, R_1 = phenyl), also provides other taxane derivatives efficiently and conveniently.

The compounds of formula IV have never been described before and are therefore a further object of the invention, as intermediates useful for the synthesis of taxane derivatives.

The following Examples illustrate the invention in greater detail.

<u>Example 1</u> — Preparation of 7,10-bis-trichloroacetyl-10-deacetylbaccatin III.

A solution of 10 g of 10-deacetylbaccatin III (18.4 mmol) in 125 ml of dry methylene chloride and 42 ml of pyridine is added dropwise with 4.77 ml of trichloroacetic anhydride (42.32 mmol). The reaction mixture is stirred for three hours or anyhow until completion of the reaction, checked by TLC on silica gel using a 5:5 n-hexane/ethyl acetate mixture as eluent. Upon completion of the reaction, 5 ml of methanol are added to destroy the

trichloroacetic anhydride excess, then water. The organic phase is thoroughly washed with HCl (0.1 M solution in water) to remove pyridine, whereas the remaining organic phase is dried over $MgSO_4$ and concentrated to dryness under vacuum. A pale yellow solid (17 g) is obtained, which upon crystallization from chloroform shows the following chemical and spectroscopical characteristics: IR (KBr) 3517, 1771, 1728, 1240, 981, 819, 787, 675 cm^{-1}; ^1H-NMR (200 MHz); δ 8.11 (Bz AA'), 7.58 (Bz C), 7.46 (Bz, BB'), 6.50 (s, H-10), 5.72 (m, H-H-2), 5.02 (d, J = 8 Hz, H-5), 4.95 (m, H-13), 4.37 (d, J = 8 Hz, H-20a), 4.18 (d, J = 8 Hz, H-20b), 4.02 (d, J = 6 Hz, H-3), 2.32 (s, 4-Ac), 2.22 (s, H-18), 1.91 (s, H-19), 1.25 and 1.11 (s, H-16, H-17), m.p. = 172-175°C, $[\alpha]_D$-36°(MeOH; C = 0.6).

Example 2 — Preparation of 13-(2-(4-methoxyphenyl)-N-benzoyl-4-phenyl-oxazolidyl-)-10-deacetylbaccatin III.

17 g of 7,10-bistrichloroacetyl-10-deacetylbaccatin III are dissolved in 250 ml of anhydrous toluene and added under stirring with 12.6 g of 2-(4-methoxyphenyl)-N-benzoyl-4-phenyl-oxazolidine-5-carboxylic acid and 6 g of DCC. After stirring overnight at 40°C, the reaction mixture is filtered and concentrated to dryness. The residue is dissolved in 300 ml of methanol/tetrahydrofuran and added with 24 ml of a 2M NH_3 aqueous solution. After 1.5 hours at room temperature the reaction mixture is concentrated to small volume under vacuum, then diluted with water and the whole is extracted with ethyl acetate. The extract is concentrated to dryness and the residue is purified on a silica gel column, eluting the product with a 1:1 ethyl acetate/petroleum ether mixture, to obtain 16.8 g of the title product with m.p. 135°C and $[\alpha]_D$ = -58° (MeOH, C = 0.5).

Example 3 — Preparation of 13-(2-(4-methoxyphenyl)-N-benzoyl-4-phenyl-oxazolidyl)-baccatin III.

A solution of 13.7 g of the product of example II in 200 ml of tetrahydrofuran is added with 56 ml of a 10% suspension of $CeCl_3.7H_2O$ in tetrahydrofuran, followed by 5.5 ml of acetic anhydride. After stirring overnight at room temperature, the reaction mixture is filtered, the filtrate is treated with methanol and concentrated to small volume; the mixture is diluted with H_2O and the product is extracted with ethyl acetate, to obtain 12 g (84%) of 13-(2-(4-methoxybenzilydene)-N-benzoyl-4-phenyl-oxazolidyl-)-baccatin III having the following physical and spectroscopical characteristics:

^{1}H-NMR: 8.07 (d, Bz), 7.60-7.19 (m, aromatic), 7.48 - 6.90 (AA', BB', p-OMePh), 6.33 (s, H-10), 5.67 (d, J = 5 Hz, H-2), 5.56 (br s, H-3'), 4.93 (d, J = 8 Hz, H-5), 4.90 (br s, H-2'), 4.45 (m, H-7), 4.28 (d, J = 8 Hz, H-20a), 4.16 (d, J = 8 Hz, H-20b), 3.82 (s, OMe), 2.27 (s, Ac), 2.08 (s, OAc), 1.66 (s, H-19), 1.29 - 1.16 (s, H-16, H-17), m.p. 146°C, $[\alpha]_D$ = -62° (MeOH, C = 0.8).

Example 4 – Preparation of Paclitaxel

12 g of 13-(2-(4-methoxyphenyl)-N-benzoyl-4-phenyl-oxazolidyl)-baccatine III are dissolved in 50 ml of tetrahydrofuran and added at 0°C with 5 ml of formic acid; the reaction mixture is left under stirring at 0°C for three hours, then diluted with water; formic acid is neutralized with $KHCO_3$ and the suspension is repeatedly extracted with ethyl acetate. The ether-acetic extracts are washed with water and concentrated to small volume. Upon crystallization from the same solvent, 10.5 g of Paclitaxel are obtained having the same chemical-physical and spectroscopical characteristics as described in literature.

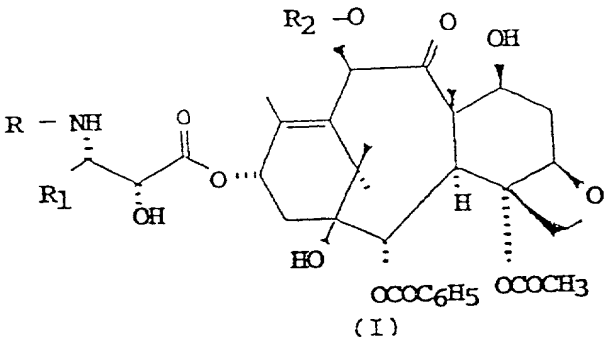
Example 5: Preparation of Docetaxel.

17 g of 7,10-bistrichloroacetyl-10-deacetylbaccatin III are dissolved in 250 ml of anhydrous toluene and added

under stirring with 11.6 g of 2-(4-methoxyphenyl)-N-tert.butoxycarbonyl-4-phenyl-oxazolidine-5-carboxylic acid and 6 g of DCC. After stirring overnight at 40°C, the reaction mixture is filtered and concentrated to dryness. The residue is dissolved in 300 ml of methanol/tetrahydrofuran and added with 24 ml of a 2M NH_3 aqueous solution. After 1.5 hours at room temperature, the reaction mixture is concentrated to small volume under vacuum, then diluted with water and the whole is extracted with ethyl acetate. The extract is concentrated to dryness and 10 g of this residue are dissolved in THF and added at 0°C with 5 ml of formic acid. The reaction mixture is left under stirring at 0°C for three hours, then diluted with water; formic acid is neutralized with $KHCO_3$, the suspension is repeatedly with ethyl acetate. The organic extracts are washed with water and concentrated to small volume. Upon crystallization from the same solvent, 9.2 g of Docetaxel are obtained having the same chemical, physical and spectroscopical characteristics as described in literature.

CLAIMS

1. A process for the preparation of the compounds of formula I



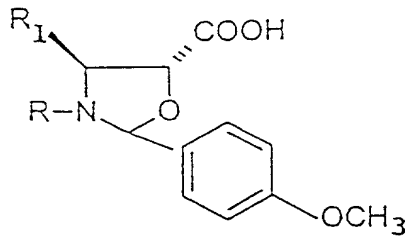
(I)

wherein R is tert.butoxycarbonyl, benzoyl or the residue of a straight or branched aliphatic acid, R_1 is phenyl or a straight or branched alkyl or alkenyl and R_2 is hydrogen or acetyl,

which comprises:

a) simultaneous protection of the hydroxyl groups at the 7- and 10- positions of 10-deacetylbaccatin III with trichloroacetic derivatives;

b) subsequent esterification of the hydroxyl group at the 13- position by reaction with a compound of formula (VII):



(VII)

wherein R is tert.butoxycarbonyl, benzoyl or the residue of a straight or branched aliphatic acid and R_1 is phenyl

or a straight or branched alkyl or alkenyl;

c) removal of the trichloroacetyl protective groups;

d) optional selective acetylation of the hydroxyl group at the 10- position;

e) acid hydrolysis of the oxazolidine ring.

2. A process as claimed in claim 1, in which step b) is effected in the presence of a condensing agent and of a base.

3. A process as claimed in claim 2 in which the condensing agent is dicyclohexylcarbodiimide and the base is pyridine.

4. A process according to any one of the above claims, in which the trichloroacetoxy groups at the 7- and 10-positions are removed by treatment with NH_4OH/NH_4Cl in aliphatic solvents.

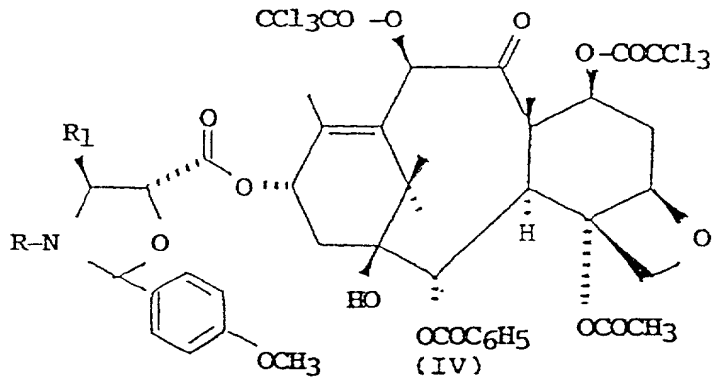
5. A process according to any one of the above claims, in which the selective acetylation of step d) is carried out by reaction with acetic anhydride in the presence of cerium III, scandium or ytterbium salts.

6. A process according to any one of the above claims, in which step e) is effected with organic or inorganic acids in aliphatic alcohols or tetrahydrofuran.

7. A process as claimed in claim 6, in which the hydrolysis is carried out with formic acid.

8. A process according to any one of the above claims, for the preparation of Paclitaxel (R = benzoyl, R_1 = phenyl, R_2 = acetyl) or Docetaxel (R = tert.butoxycarbonyl, R_1 = phenyl, R_2 = H).

9. Intermediates of formula IV



wherein R and R_1 are as defined in claim 1.

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DECLARATION AND POWER OF ATTORNEY

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below at 201 et seq. underneath my name.

I believe I am the original, first and sole inventor if only one name is listed at 201 below, or an original, first and joint inventor if plural names are listed at 201 et seq. below, of the subject matter which is claimed and for which a patent is sought on the invention entitled

A process for the preparation of taxanes from 10-deacetylbaccatin III

and for which a patent application:
□ is attached hereto and includes amendment(s) filed on *(if applicable)*
□ was filed in the United States on as Application No. *(for declaration not accompanying application)*
with amendment(s) filed on *(if applicable)*
□ was filed as PCT international Application No. on and was amended under PCT Article 19 on *(if applicable)* PCT/EP00/01471 23.02.2000

I hereby state that I have reviewed and understand the contents of the above identified application, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, §1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, §119(a)-(d) of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

EARLIEST FOREIGN APPLICATION(S), IF ANY, FILED PRIOR TO THE FILING DATE OF THE APPLICATION			
APPLICATION NUMBER	COUNTRY	DATE OF FILING (day, month, year)	PRIORITY CLAIMED
MI99A000417	Italy	02.03.1999	YES ☒ NO □
			YES □ NO □

I hereby claim the benefit under Title 35, United States Code, §119(e) of any United States provisional application(s) listed below.

APPLICATION NUMBER	FILING DATE

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code §112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, §1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application:

APPLICATION SERIAL NO.	FILING DATE	STATUS		
		PATENTED	PENDING	ABANDONED

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	POST OFFICE ADDRESS	STREET	CITY	STATE OR COUNTRY	ZIP CODE
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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

SIGNATURE OF INVENTOR 201	SIGNATURE OF INVENTOR 202	SIGNATURE OF INVENTOR 203
DATE 31-07-2001	DATE	DATE
SIGNATURE OF INVENTOR 204	SIGNATURE OF INVENTOR 205	SIGNATURE OF INVENTOR 206
DATE	DATE	DATE